REMARKS

Claims 1-16 and 19-20 are pending in this application. By the Office Action, claims 17-18 are withdrawn from consideration; and claims 1-16 are rejected under 35 U.S.C. §103. By this Amendment, claims 17-18 are canceled and claims 19-20 are added. Support for new claims 19-20 can be found in at least claims 1, 17 and 18 as filed.

I. Claim for Priority

A Claim for Priority with a certified copy of the priority application was filed on January 5, 2004. Applicant has not yet received from the Examiner acknowledgment of receipt of the certified copy of the priority application. The Examiner is requested to acknowledge receipt of the certified copy in the next Office Action.

II. Restriction Requirement

Claims 17-18 are withdrawn from consideration. The Office Acti0on notes that Applicants' representative elected Group I, claims 1-16, without traverse. This is incorrect. In response to the telephone Restriction Requirement, Applicants' representative specifically elected Group I, claims 1-16, with traverse. No formal traversal was provided at the time of election as the specific reasons for restriction were not of record.

Nevertheless, claims 17-18 are canceled herein. In their place, new claims 19-20 are added. New claims 19-20 generally correspond to claims 17-18, but are specific to the production of the sustained release pharmaceutical composition of claim 1. Claims 19-20 should be examined and allowed with Group I.

Where product and process claims are presented in the same application, Applicant may be called upon under 35 U.S.C. §121 to elect claims to either the product or the process. MPEP §821.04. However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim depends from or otherwise includes all the limitations of an allowed product claim. Id.

In the present application, the method claims 19-20 include all of the limitations of the product of Group I. In particular, all of the limitations of the independent product claim 1 of Group I are incorporated into the method claims 19-20.

Since the method claims 19-20 include the limitations of the product claims of Group I, the method claims must be rejoined with the product claims once the product claims are allowed. Thus, to streamline prosecution and avoid delay, the Restriction Requirement should be withdrawn to permit concurrent examination of all of the pending claims.

Applicants respectfully request reconsideration and withdrawal of the Restriction Requirement.

III. Election of Species

The Office Action also requires an election of species to a specific cephalosporin antibiotic of claim 6.

In response to the Election of Species Requirement, Applicants hereby elect species Cephalexin. This election is made with traverse.

In further response to the Election of Species Requirement, Applicants respectfully assert that at least claims 1, 6 and 19-20 are generic to the elected species. Furthermore, Applicants respectfully assert that at least claims 1-16 and 19-20 read on the elected species.

Applicants traverse the Election of Species Requirement on the ground that the generic claims are not so broad as to place an undue burden on the Patent Office to search and examine the full scope of the claims. Rather, Applicants respectfully assert that search and examination of the entire application could be conducted without undue burden on the Examiner, thus avoiding delay and expense to Applicants.

Applicants further understand, however, that upon search, examination and allowance of the elected species, search and examination will continue as to the non-elected species within the scope of the generic claims.

IV. Rejection Under 35 U.S.C. §103

The Office Action rejects claims 1-16 under 35 U.S.C. §103(a) over Arora and Zhang. Applicants respectfully traverse this rejection.

The Office Action cites Arora and Zhang as variously disclosing sustained release pharmaceutical compositions. The Office Action argues that it would have been obvious to combine the cited references to practice the claimed invention. Applicants respectfully disagree, at least because the references are improperly combined, and either combined or individually would not have rendered obvious the claimed invention.

Arora discloses a modified release pharmaceutical composition in the form of a tablet of cephalexin or cefaclor and a mixture of hydrophilic polymer of different viscosity. Abstract. The combination of polymers mentioned in the reference for the modified release matrix formulation is hydroxypropylcellulose. Abstract; claim 1. As is known in the art, hydroxypropylcellulose such as those described in Arora are semi synthetic derivatives of cellulose, such as cellulose ethers with hydroxypropyl substitutions. *See* Richard J. Lewis, Sr., *Hawley's Condensed Chemical Dictionary, 13th Ed.*, p. 599 (1997) (copy attached). These hydroxypropylcellulose are hydrophilic polymers, which are not only structurally similar to each other (hydroxypropyl substituted cellulose ethers) but also have similar properties and behavior in the aqueous system. Thus, the behavior can be readily predicted whether used alone or in combinations of two or more.

Zhang discloses a formulation of pharmaceutical itself and a three component release rate controlling matrix composition. Abstract. The three components of matrix composition are: 1) a pH dependent gelling polymer such as alginate component; 2) a Enteric polymer component such as Eudragit L or S; and 3) A pH independent gelling polymer such as hydroxy propyl methylcellulose or polyethylene oxide. Abstract.

However, neither Arora nor Zhang, alone or in combination, disclose the specific composition of instant claim 1. Claim 1 is directed to a sustained release pharmaceutical composition comprising a cephalosporin antibiotic, a mixture of polymers comprising of galactomannans and neutral swellable polymers, and other pharmaceutically acceptable excipients. Such a composition is nowhere taught or suggested by the cited references.

A. The References Do Not Teach or Suggest the Claimed Polymers

Claim 1 specifically requires a mixture of polymers comprising of galactomannans and neutral swellable polymers. Such a mixture is not taught or suggested by Arora and/or Zhang.

According to the claimed invention, the combination of polymers is distinctly different from the polymers of the cited references. The claimed polymers belong to different chemical classes than the polymers of the cited references, and thus provide different effects and properties in the gastric fluids in which the pharmaceutical composition is used.

For example, Xanthan gum is one example of a galactomannas required in claim 1. Such galactomannas as Zanthan gum is a naturally occurring anionic hetropolysaccharide gum derived from the aerobic fermentation with the organism Xanthomonas campestris. *See* Richard J. Lewis, Sr., *Hawley's Condensed Chemical Dictionary, 13th Ed.*, p. 1186 (1997) (copy attached); Susan Budavari, Ed. *The Merck Index, 12th Ed.*, p. 1718 (1996) (copy attached). It contains D-glucose, D- mannose, D-glucuronate in the molar ratio of 2.8: 2.0 : 20 and is partially acetylated with about 4.7% acetyl. Id. As is known in the art, Zanthan gum is a viscolyzing agent, which helps to maintain the integrity of dosage form along with helping the sustained release of the drug from the matrix.

The other polymer required in the claimed invention is a neutral swellable polymer. One example of such a neutral swellable polymer used in the invention is Eudragrit NE 30 D

(a poly(ethyl acrylate : methyl methacrylate) in a ratio of 2 :1), which is basically a methacrylic ester copolymer.

The two types of polymers required in the composition of claim 1 are chemically very different from the polymers of the cited references and from each other. As a result, they also differ in their physical characteristics, chemical properties, and effects and properties in the gastric fluids. Generally, the galactomannans such as Xanthan gum are soluble in water, whereas the neutral swellable polymers such as Eudragrit NE 30 D remains water insoluble throughout the entire pH range in the gastro intestinal tract. Neither Arora nor Zhang teach or suggest that such a combination of polymers should or could be used to provide a suitable sustained release pharmaceutical composition, as claimed.

Because the two required polymers have different properties, it would not have been obvious to the person skilled in the art to predict how a combination of the polymers would behave in the varying chemical environment along the gastro intestinal tract. Nor would it have been obvious to the person skilled in the art to predict how such a combination would affect the release mechanism. Whereas Arora uses two similar hydroxypropylcelluloses, which have similar and thus generally predictable combination properties, the teachings of Arora could not be readily extrapolated to the claimed invention. One of ordinary skill in the art would not have been motivated to change the compositions of Arora and Zhang to arrive at the claimed invention.

In fact, it was surprisingly found that when a tablet comprising the claimed composition comes in contact with aqueous media of the gastrointestinal tract, the thin film of neutral swellable polymers (such as poly (ethyl acrylate : methyl methacrylate)) controls the penetration of initial erosion of the galactomannans (such as Xanthan gum), which is high at acidic pH. The neutral swellable polymer slowly hydrates without disrupting the hydrophilic composition formed by the hetropolysaccharide. The insoluble neutral swellable polymer

forms a sponge like structure, which behaves as an inert matrix. Once the galactomannans is completely hydrated, it forms a gel and then the release of active ingredient is governed by diffusion of dissolved drug through the pores, channels and capillaries of the insoluble polymer composition.

Moreover, the claimed invention provides a distinct advantage over the compositions of the cited references. The synergistic combination of galactomannans and neutral swellable polymers (such as xanthan gum and Eudragit NE30D (poly (ethyl acrylate : methyl methacrylate) 2:1) provides an improved control over the rate of release of the drug from the matrix, which benefits therapy by producing constant blood levels of the drug (such as cephalexin) for durations long enough to decrease the frequency of dosing from twice daily to once daily. Reduced frequency of dosing (such as from twice daily to once daily) improves the patient compliance to the treatment and at the same time minimizes the side effects associated with the therapy. In contrast, at least Arora is directed to twice daily dosing.

B. The References Do Not Teach or Suggest Release Rate Control for Cephalosporins

Claim 1 also specifically requires that the sustained release pharmaceutical composition comprises a cephalosporin antibiotic. The composition must thus as a whole provide for sustained release of at least cephalosporin antibiotic in particular. However, at least Zhang does not teach or suggest sustained release compositions that are applicable to cephalosporin antibiotics.

In contrast to the claimed invention, the rate controlling combination of the three polymer composition of Zhang is used for the different type of drug, namely pentoxyfilline and verapamil. Both of pentoxyfilline and verapamil have different physical, chemical, and pharmacological properties from the claimed cephalosporin antibiotics. Thus, it would not have been obvious for one or ordinary skill in the art to have looked to the sustained release

composition of Zhang to modify the otherwise acceptable sustained release composition of Arora, to practice the claimed invention. It would not have been obvious to a person skilled in the art that a drug of different physical and pharmacological properties would behave in the same manner in a different rate controlling polymer system.

The substantial difference between the rate controlling polymer combination used in the claimed invention and Zhang is further explained below for an embodiment of the claimed invention using Zanthan gum and Eudragit NE30D (poly (ethyl acrylate : methyl methacrylate) 2:1) as the galactomannans and neutral swellable polymers.

The rate controlling matrix of the invention contains a galactomannans such as Xanthan gum, which is naturally derived viscolyzing agent and hydrophilic in nature. This is a pH dependent polymer because it disperses in the acidic media and swells up in the alkaline media. The other copolymer used in combination with the galactomannans is a neutral swellable polymers (such as Eudragit NE30D (poly (ethyl acrylate : methyl methacrylate) 2:1)), which is different from eudragit L or S of Zhang. Eudragit L or S chemically is a methacrylic acid derivative, which is soluble in the alkaline pH environment present in the lower part of the gastrointestinal tract (i.e. in the intestine). Eudragrit NE30D (poly (ethyl acrylate : methyl methacrylate) 2:1) chemically is a methacrylic ester copolymer. This copolymer is insoluble throughout the entire pH range of the gastrointestinal tract.

According to the claimed invention, the release of the drug from the matrix is not because of the erosion of the polymer at alkaline pH, which happens in the case of Eudragit L or S in Zhang (which dissolves in the alkaline pH). In the claimed invention, the release of the drug is released largely through diffusion from the pores or capillaries formed in the insoluble neutral swellable polymer (such as Eudragit NE30D).

Therefore, it would not have been obvious to the person skilled in the art that how a sustained release matrix would perform and what the sustained release profile would be under

different properties of the polymers used. It was surprisingly discovered by the present inventors that when a tablet comes in contact with aqueous media of the gastrointestinal tract, the thin film of neutral swellable polymers (such as xanthan gum and Eudragit NE30D (poly (ethyl acrylate : methyl methacrylate) 2:1)) controls the penetration of initial erosion of galactomannans (such as xanthan gum), which is high at acidic pH. The poly (ethyl acrylate : methyl methacrylate) 2:1 slowly hydrates without disrupting the hydrophilic composition formed by the hetropolysaccharide. The insoluble poly (ethyl acrylate : methyl methacrylate) 2:1 forms a sponge-like structure, which behaves as an inert matrix. Once the xanthan gum is completely hydrated, it forms a gel and then the release of active ingredient is governed by diffusion of dissolved drug through the pores, channels and capillaries of insoluble polymer composition.

Moreover the claimed invention has a distinct advantage over Zhang in the same manner as described for Arora above. In particular, the sustained drug release profile of the claimed invention helps in reducing the dosage frequency from twice daily to once daily. The synergistic combination of galactomannans and neutral swellable polymers (such as xanthan gum and Eudragit NE30D (poly (ethyl acrylate : methyl methacrylate) 2:1)) provides an improved control over the rate of release of the drug from the matrix, which benefits therapy by producing constant blood levels of the drug (cephalexin) and by decreasing frequency of dosing from twice daily to once daily. Reduced frequency of dosing (such as to once daily) improves the patient compliance to the treatment and at the same time minimizes the side effect associated with the therapy.

C. Conclusion

For at least these reasons, the claimed invention would not have been obvious over the cited references. The cited references would not have led one of ordinary skill in the art to combine their respective teachings, and modify the resultant combination to practice the

claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

V. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of claims 1-6, 8, 12-13 and 21-22, and rejoinder and prompt allowance of claims 14-15 and 17-20, are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

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Attachments:

Richard J. Lewis, Sr., *Hawley's Condensed Chemical Dictionary, 13th Ed.*, pp. 599, 1186 (1997).
Susan Budavari, Ed. *The Merck Index, 12th Ed.*, p. 1718 (1996).

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